

## REMARKS

### Amendments to the Claims

Claims 1-9 and 14 are under examination with entry of the present Amendment. Claim 2 has been cancelled without prejudice. The claim dependency of claim 3 has been amended. Claim 1 has been amended as set out below.

Amended claim 1, which incorporates the subject matter of cancelled claim 2, recites a therapeutic composition comprising IgY polyclonal antibodies obtained from an egg laid by a fowl which has been immunized with one or more of gliadin, HMG and LMG, wherein the IgY polyclonal antibodies are capable of specifically binding to gliadin, HMG, LMG and mixtures thereof in the gastrointestinal tract of a subject; and a physiologically acceptable carrier, excipient or diluent; and wherein the IgY polyclonal antibodies upon oral administration to the subject inhibit transport of gliadin, HMG, LMG into the mucosal membrane of the gastrointestinal tract of the subject. Support resides in the as-filed specification for example, on pages 5-14.

No new matter has been added with the amendments made herein. Support for the amended claims is found throughout the application and in the as-filed claims.

### Rejections under 35 U.S.C. §103

The Office Action has maintained the rejection of claims 1-9 and 14 as allegedly unpatentable over Lee (U.S. Patent No. 5,367,054) in view of Ellis *et al.* (Gut, 1998, 43:190-195) for the reasons provided on pages 3-5 of the Office Action. The Office Action states that:

given that Ellis *et al.* teach using the anti-gliadin antibody containing composition for immunodetection and the teaching by Lee on the advantage of making IgY antibodies i.e., that egg yolk is a very good source of specific antibodies and that the antibodies are more specific (see column 1, lines 34-46), one of ordinary skill in the art would have been motivated to make the anti-gliadin antibodies for immunodetection as IgY antibodies for the high specificity offered by the egg yolk.

Applicants respectfully traverse this rejection for the reasons set forth below. This amendment is accompanied by a Declaration from inventor Hoon Sunwoo. Applicants respectfully request entry and consideration of this Declaration. The Declaration is included to establish that there are distinctions between Applicants' claimed invention and the cited prior art. The Declaration supports that the IgY polyclonal antibodies have been formulated to provide unpredictable results - not only in addition to the high specificity contended by the Office Action. The IgY polyclonal antibodies to gluten components have not been previously described in the prior art, and do not constitute a predictable result of known elements. The Declaration provides further evidence from the perspective of one skilled in the art that the IgY polyclonal antibodies have been specifically formulated so as to be capable of specifically binding to gluten in the gastrointestinal tract of a subject. This characteristic or activity of IgY polyclonal antibodies is not taught or suggested by the cited prior art.

The IgY polyclonal antibodies are specific to particular gluten components (i.e., gliadin, high molecular glutenin (HMG), low molecular glutenin (LMG), or mixtures thereof), wherein the IgY polyclonal antibodies inhibit the transport of gliadin, HMG, and LMG into the mucosal membrane of the gastrointestinal tract upon oral administration to a subject. As described in the as-filed specification,

The therapeutic effect of the present invention is mediated by blocking glutes contained in foodstuffs before they are transported across the epithelial layer in intestines. With typical celiac disease, intact gluten is permeated into mucosal membrane without digestion. By binding to gluten with anti-gluten antibodies, gluten is passed through the intestines, rather than being transported into the mucosal membrane, thereby preventing the disease-causing toxicity. The present invention may also be beneficial for gluten-sensitive people who are essentially asymptomatic or have no gastrointestinal symptomatology (paragraph [0027]).

The burden is on Applicants to show a novel or unobvious difference between the claimed IgY and the antibodies of the prior art. Applicants wish to draw the Examiner's attention that in order to better define the present invention and in an effort to expedite prosecution, the language of amended claim 1 limits the claim to a specific antibody isotype, IgY. Applicants have specifically amended the claims to exclude therapeutic compositions containing IgG polyclonal antibodies. The

resulting claims are limited to an immunoglobulin isotype that is specifically exemplified in the application. On the contrary, the Office Action acknowledges that "Ellis's antibodies are not IgY antibodies." Rather, Ellis *et al.* teaches a polyclonal IgG antibody to gliadin. Although both the polyclonal IgG rabbit anti-gliadin antibody of Ellis *et al.* and the fowl-derived IgY polyclonal antibodies of the present invention exhibit the same action of binding to a component of gluten, they are different from each other with respect to not only composition of matter or type of substance, but also to mechanisms of their action.

Those skilled in the art recognize that these isotypes of antibodies are not interchangeable, and would not, based on the references themselves, substitute IgG for IgY polyclonal antibodies. As discussed in Applicants' response of November 27, 2008, avian IgY differs structurally from mammalian IgG, particularly in the constant region which renders IgY much less antigenic than IgG. Significant differences in the physical and chemical properties of IgY and IgG (i.e., amino acid composition, electrophoretic mobility, isoelectric pH value, molecular weight, chemical stability, reaction to ionic detergents and salt solutions) were set out in Applicants' response of November 27, 2008.

Generally speaking, a polyclonal antibody is a composition comprising various kinds of antibodies produced by many clones against different epitopes on an antigen molecule. Thus, a polyclonal antibody is not considered to be a single compound (protein) with respect to the structure of an antibody molecule. Applicants' IgY polyclonal antibodies specific to gluten components bind to and aggregate the gluten components, thus inhibiting their active or passive transport across the mucosal membrane of the gastrointestinal tract. Because of the polyclonal nature of the antibodies, more epitopes are recognized; thus, entrapment and clearance of the gluten components are more readily instigated. In this respect, polyclonal antibodies are different than monoclonal antibodies. However, despite disclosing a polyclonal IgG rabbit anti-gliadin antibody, the Ellis *et al.* reference, in fact, teaches away from the use of polyclonal antibodies:

Polyclonal antibody based assays suffer a lack of specificity (page 190, col. 2, paragraph 1).

...

The low sensitivity of the assay to  $\omega$  gliadins is probably due to the low reactivity of polyclonal antigliadin antiserum to  $\omega$  gliadins (page 193, col. 2, fifth paragraph).

Applicants further note that it is the position of the Examiner that Lee be the primary reference. In other words, the Examiner alleges that one skilled in the field of the invention would have been led directly to the present invention by modifying the teachings of Lee in view of Ellis *et al.* However, Lee provides merely general teachings of antigens, with particular emphasis only on anti-bacterial antibodies:

Suitable antigens include, for example, bacterial species or subtypes including but not limited to the following: *Staphylococcus aureus*; *Staph. epidermidis*; *Streptococcus pyogenes*, A. type 1, type 3, type 5, type 8, type 12, type 14, type 18, and type 22; *Aerobacter aerogenes*; *Escherichia coli*; *Salmonella enteritidis*; *Pseudomonas aeruginosa*; *Haemophilus influenzae*; *Strep mills*; *Proteus vulgaris*; *Shigella dysenteriae*; *Diplococcus pneumoniae*; *Propionbacter aches*; *Strep sanguis*; *Strep salivarius*; and *Strep mutans*. The selection of other suitable antigens is within the knowledge of one of ordinary skill in the art (col. 8, lines 16-26).

Neither Lee nor Ellis *et al.* discloses the particular selection of IgY polyclonal antibody (i.e., an IgY antibody specific to gliadin, HMG and LMG and obtained from fowl), wherein the antibodies are capable of specifically binding to gluten component and mixtures thereof in the gastrointestinal tract of a subject, as recited in amended claim 1. As such, Applicants assert that without the improper hindsight, it would not have been obvious to prepare IgY polyclonal antibodies to the specific gluten components as presently claimed which are effective in the inhibition of transport of gluten into the mucosal membrane when orally administered to a subject.

The language of amended claim 1 recites that "the IgY polyclonal antibodies are capable of specifically binding to gliadin, HMG, LMG and mixtures thereof in the gastrointestinal tract of a subject." The Declaration of Hoon Sunwoo provides further evidence of this characteristic or ability of the IgY polyclonal antibodies, which is not taught or suggested by the cited prior art.

Ellis *et al.* teaches the ability of the polyclonal IgG rabbit anti-gliadin antibody only to act as a capture antibody in a sandwich ELISA for detection of gluten in foods. Plates are coated with more capture protein than can actually be bound during the assay in order to facilitate the largest

working range of detection possible. The binding of the polyclonal IgG rabbit anti-gliadin antibody *in vitro* does not predict that a similar effect will be observed in the gastrointestinal tract, and has no relation to the effect of inhibiting transport of gluten into the mucosal membrane *in vivo*, as claimed in the present invention. Ellis *et al.* does not teach or suggest the direct administration of antibodies to "immunize" a subject so as to inhibit the transport of gluten into the mucosal membrane. In fact, Ellis *et al.* discloses use of the polyclonal IgG rabbit anti-gliadin antibody only in an *in vitro* detection method. No assumption can be made from these results on how the antibodies would treat celiac disease or a gluten sensitive condition. In view of the foregoing, Applicants submit that Ellis *et al.* teaches away from the present invention. The IgG antibodies of the prior art do not even possess the same physicochemical or functional characteristics of the IgY polyclonal antibodies of the present invention.

While Lee does teach the production of polyclonal IgY egg yolk antibodies specific to antigens, Lee presents no evidence that any of the polyclonal IgY egg yolk antibodies were directed against antigens such as gluten. The Examiner maintains that Lee is relevant art to the present invention merely because Lee show the production of IgY antibodies raised against antigens even if there is no scientific evidence that any of the IgY antibodies were directed against antigens such as gluten. The cited passage of Lee (col. 1, lines 35-47) simply discloses that the methods of Lee can result in the production of IgY egg yolk antibodies, with no inference to antibodies which bind to gluten. Neither reference teaches nor suggests what Applicants have done, which is to formulate polyclonal IgY antibodies specific to gliadin, HMG and LMG and obtained from fowl, and which are capable of specifically binding to gliadin, HMG, LMG and mixtures thereof in the gastrointestinal tract of a subject to inhibit the transport of gluten into the mucosal membrane.

There is no explicit or implicit motivation to combine the two references. Neither reference suggests nor contemplates avian IgY polyclonal antibodies specifically formulated for the treatment of celiac disease or a gluten sensitive condition, as now clearly claimed. The polyclonal IgG antibody to gliadin of Ellis *et al.* was envisaged for the detection of gluten in foods. The polyclonal IgY egg yolk antibodies described in Lee are not directed to any particular antigen except for bacterial species or subtypes.

Further, the language of amended claim 1 recites the addition of a physiologically acceptable carrier, excipient or diluent. It would have been obvious to one skilled in the art to include such ingredients in the composition only after conception of the invention, which again requires irrepressible hindsight. Neither Lee nor Ellis *et al.* discloses the addition of this ingredient with IgY polyclonal antibodies. The Declaration of Hoon Sunwoo provides evidence of the significance of inclusion of an excipient such as for example, mannitol or sorbitol, on the survival of IgY polyclonal antibodies in gastrointestinal fluids. In view of the foregoing, it is submitted that Applicants' claimed invention does not constitute a predictable use of prior art elements.

In summary, claims 1, 3-9 and 14 are not anticipated or rendered obvious in view of the cited prior art since the references do not teach or suggest the features of the invention as claimed. Reconsideration and withdrawal of the claim rejections under 35 U.S.C. §103 are thus respectfully requested.

### CONCLUSION

In view of the foregoing remarks and amendments, it is respectfully submitted that this application is in condition for allowance and allowance thereof is respectfully requested.

Respectfully submitted,

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